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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,228	11/14/2003	Luigi Grasso	MOR-0251	4529

23377 7590 04/15/2009

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,228	GRASSO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-66,68-70,73-78,81-88,91-99,135 and 136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *64, 65, 68, 75-77, 83, 84, 88, 93, 94, 97 and 139-150* is/are allowed.

6)☒ Claim(s) *62,63,66,69,70,73,74,78,81,82,85-87,91,92,95,96,98,99,135 and 136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 67 has been canceled. Claims 62, 64, 68, 73, 75, 77, 81, 83, 91, 93, 97 have been amended. Claims 139-150 have been added. Claims 62-66, 68-70, 73-78, 81-88, 91-99, 135 and 136 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 98 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 98 further limits the scope of claim 96 as it contains a limitation which is requires for claim 91.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62, 63, 66, 69, 70, 73, 74, 78, 81, 82, 85-87, 91, 92, 95, 96, 98, 99, 135 and 136 are rejected under 35 U.S.C. 103(a) as being obvious over Nicolaides et al (U.S. 6,808,894) in view of Borreback et al (Adv Drug Del Rev, 1988, Vol. 2, pp. 143-165).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides teach the elements of the instant claims with regard to anti-sense inhibition of PMS2 and with regard to the administration of dominant negative PMS2 (column 3, lines 29-41, column 4, lines 1-10). Nicolaides et al teach restoring genetic stability to the host after selection of hybridoma cells with the desired traits (Example 5). Nicolaides et al do not teach obtaining an antibody producing cell by in vitro immunization, or the specific "removal" of the anti-sense nucleic acids..

Borreback et al teach that in vitro immunization has great advantages over conventional means of obtaining monoclonal antibodies because in vitro immunization require only small amounts of antigen, and has the potential to produce an antibody against an epitope that fails to provoke an antibody by conventional administration. Borreback et al teach that in vitro immunization can be used to make a human antibody because it bypasses the requirement for sensitizing patients (page 144 under "Summary").

It would have been prima facie obvious at the time that the invention was made to use hybridomas or antibody producing lymphocytes for the antibody producing cells of Nicolaides.

One of skill in the art would have been motivated to do so by the teachings of Borreback et al on the advantages of producing antibodies by the method. It would have been further obvious that the hybridoma cells need not be maintained with the anti-sense nucleic acids after antibody formation has occurred. One of skill in the art would have been motivated to not continue the exposure of the hybridoma to the anti-sense nucleic acid because Nicolaides teaches the restoration of "genetic stability" of the hybridoma and because the anti-sense nucleic acids are expensive and there is no need to continue the exposure of the hybridoma to the antisense nucleic acid once antibody secretion has occurred. Further Nicloaides teach the exposure of the cells to dominant negative inhibitor of PMS2 by an inducible expression vector and the restoration of genetic stability once a cell line is produced that contains the desired genetic alterations by removal of the inducers used to activate the promoter of the inducible vectors (column 36, lines 12-24). Thus it would be obvious to one of skill in the art to "remove" the chemical inhibitor of mismatch repair based on the teachings of Nicolaides.

It is noted that the phrase "wherein said antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells have an affinity for said antigen of at least about $1 \times 10^{7}\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$" and the phrase "wherein said hypermutated hybridoma cells that produce antibodies in greater titers than said parental hybridoma cells have a titer that is at least about 1.5-8-fold greater than the titer produced by said parental hybridoma cells" is not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 62, 63, 66, 69, 70, 73, 74, 78, 81, 82, 85-87, 91, 92, 95, 96, 98, 99, 135 and 136 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,808,894 in view of Borreback et al (Adv Drug Del Rev, 1988, Vol. 2, pp. 143-165) and Yelton et al (Journal of Immunology, 1995, Vol. 155, pp. 1994-2004).

Claims 1-6 of the '894 patent are drawn to methods for making hypermutable antibody-producing cells in vitro, by means of introducing into said antibody producing cell a polynucleotide comprising a dominant-negative allele of a mismatch repair gene, wherein said allele is a truncated mutant of PMS2, and wherein said antibody producing cell become hypermutable. Claim 12 of the patent requires the restoration of genetic stability of the hypermutable cell, but does not specify "removal" of the chemical inhibitor of mismatch repair. Claims 13 and 16 of the '894 patent disclose that the antibody produced have increase affinity for antigen. Claims 18 and 20 of the '894 patent disclose that the antibodies are produced in an increased titer. The claims do not specify a method for producing hypermutable hybridoma cells resulting from in vitro immunized immunoglobulin producing cells, nor do the claims teach the introducing of an antisense nucleic acid to PMS2. or the screening for antibodies of higher affinity or higher titer.

Borreback et al teach that in vitro immunization has great advantages over conventional means of obtaining monoclonal antibodies because in vitro immunization require only small

amounts of antigen, and has the potential to produce an antibody against an epitope that fails to provoke an antibody by conventional administration. Borreback et al teach that in vitro immunization can be used to make a human antibody because it bypasses the requirement for sensitizing patients (page 144 under "Summary").

Yelton et al teach that increasing antibody affinity 10-fold provides a 2.5 to 3.0-fold therapeutic advantage in anti-tumor activities (page 2002, second column, lines 8-13 and lines 19-23). Yelton et al teach the cloning of hybridoma DNA into a cell expression system using codon based mutagenesis and the selection of higher affinity antibodies produced from the expression of the mutated hybridoma antibody genes (page 1995, Figure 1).

Evan et al teach that tetracycline inducible systems are well known in the art (column 25, line 66 to column 26, line 3).

It would have been prima facie obvious at the time that the invention was made to use hybridomas or antibody producing lymphocytes for the antibody producing cells of Nicolaides. One of skill in the art would have been motivated to do so by the teachings of Borreback et al on the advantages of producing antibodies by the method. It would also have been obvious that inhibition of expression of PMS2 would have the same effect on the antibody-producing cell as that of the dominant negative mutant which interferes with the activity of the PMS2 protein. One of skill in the art would know that a protein can be inhibited by reducing the activity of said protein by means of an antagonists such as a dominant negative version of the protein, or by reducing the level of transcribe d protein by administering antisense nucleic acids. It would have been further obvious that the hybridoma cells need not be maintained with the anti-sense nucleic acids after antibody formation has occurred. One of skill in the art would have been motivated to not continue the exposure of the hybridoma to the anti-sense nucleic acid because Nicolaides teaches the restoration of "genetic stability" of the hybridoma and because the anti-sense nucleic acids are expensive and there is no need to continue the exposure of the hybridoma to the antisense nucleic acid once antibody secretion has occurred. Additionally , it would have been obvious that the dominant negative allele of PMS2 would have been under the control of an inducible promoter in order that claim 12 of the patent, requiring the restoration of genetic stability could be carried out by removal of the inducer because such means for control expression are well known in the art as exemplified by Evans et al.

It would also have been obvious to screen for antibodies having higher affinity based on the teachings of Yelton et al and claims 13 and 16 of the '894 patent which indicate that antibodies with increased affinities are produced. It would have been obvious to screen for antibody producing cells producing antibodies at a higher titer based on claims 18 and 20 which indicate that antibody-producing cells producing antibodies at a higher titer result from the method of making a hypermutable antibody producing cell.

Claims 64, 65, 68, 75-77, 83, 84, 88, 93, 94, 97 and 139-150 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643